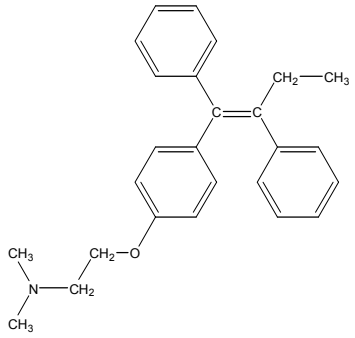
TAMOXIFEN
CAS No. 10540-29-1
First listed in the *Ninth Report on Carcinogens*



CARCINOGENICITY

Tamoxifen is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between exposure to tamoxifen and cancers of the uterine endometrium. However, there is also conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer, and may prevent or delay the occurrence of breast cancer in women at increased risk for this disease.

The potential effect of tamoxifen in increasing the risk of endometrial cancer has been reported in one adequate cohort study, four adequate case-control studies, and 14 randomized clinical trials.

The cohort study (Curtis et al., 1996) examined the effect of tamoxifen on risk of endometrial cancer in 87,323 women with breast cancer reported to the Surveillance, Epidemiology and End Results (SEER) program in the United States and found a statistically significant elevation of endometrial cancer in women who had received tamoxifen therapy. In two of the four case-control studies (Sasco et al., 1996; van Leeuwen et al., 1994), a non-significant elevation of risk for endometrial cancer was found, with a significant increase in risk with increasing duration of therapy in one of these studies (van Leeuwen et al., 1994). In the U.S. case control study (Cook et al., 1995), no increase was seen, but a shorter duration of tamoxifen use was reported. In the fourth case-control study (Hardell, 1988), increased risk of endometrial cancer for tamoxifen use was found, but confounding factors could not be eliminated.

In the two largest randomized clinical trials (Fisher et al., 1994; Rutqvist et al., 1995), there was a strong and statistically significant association between risk for endometrial cancer and use of tamoxifen. In the 12 other smaller trials, no statistically significant increases in endometrial cancer were seen, although 29 endometrial cancers were reported in tamoxifen-treated individuals and 14 in controls when these 12 studies were combined.

In 32 case studies, 102 cases of endometrial cancer were reported in women who received tamoxifen for breast cancer. One case series reported significantly more high-grade endometrial tumors in tamoxifen-treated breast cancer patients than in patients without tamoxifen use (Magriples et al., 1993); this difference, however, was not seen in six other

studies.

MacMahon (1997) concluded that published results were suggestive of a causal association between tamoxifen use and endometrial cancer but were not conclusive because of confounding factors such as prior hysterectomy and/or hormone replacement therapy. Examining the same confounding factors, an IARC Working Group concluded that there is a positive association between tamoxifen use and endometrial cancer and cited several studies in support of this conclusion; the same potential confounders were considered unlikely to have a major effect on the reported relative risks (IARC, V. 66, 1996).

Experimental animal studies also provide evidence of tamoxifen's carcinogenic effects. The IARC Working Group (IARC, V. 66, 1996) reviewed experimental studies reported prior to 1996 and reached a similar conclusion. Tamoxifen, administered orally, was evaluated in one mouse study and eight rat studies. In mice, the incidences of benign ovarian and testicular tumors were significantly increased after 3 months of treatment. In rats, in eight studies that varied in treatment lengths, tamoxifen induced preneoplastic liver lesions and benign or malignant liver tumors. One rat study reported a decrease in tumors in hormone-dependent tissues, but reduced weight gain may have been a contributing factor. In one additional study where tamoxifen was given by subcutaneous administration, mammary tumor development was inhibited in intact and ovariectomized mice (reviewed in IARC, 1996).

Uterine abnormalities including endometrial carcinoma have also been reported in experimental animals exposed to tamoxifen. Rats receiving tamoxifen daily by oral gavage for 20 to 52 weeks were reported to have squamous cell metaplasia, dysplasia, and squamous cell carcinoma of the uterus while no comparable lesions were seen in controls (Mantyla et al., 1996). Short-term developmental exposure to tamoxifen on days 1to 5 of neonatal life has recently been reported to significantly increase the incidence of reproductive tract abnormalities in both female and male mice, including uterine carcinoma and seminal vesicle tumors (Newbold et al., 1996; abstr.; Newbold et al., 1997).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Several studies (reviewed by IARC V.66, 1996) described tumor initiation/promotional and co-carcinogenicity attributes of tamoxifen. In mice, tamoxifen inhibited 3-methylcholanthrene-induced cervical cancer and virus-induced leukemia. In several studies with male and female rats, it enhanced liver tumors induced by *N*-nitrosodiethylamine. In one rat study, it enhanced the development of *N*-nitrosodiethylamine-induced kidney tumors; but in a number of other studies, it inhibited 7,12-dimethyl[*a*]benzanthracene-induced mammary tumors. In hamsters, two studies reported the inhibition by tamoxifen of kidney and liver tumors induced by 17β-estradiol.

Several reports in the literature (IARC V.21, 1979) demonstrate that women receiving estrogen replacement therapy unopposed by progesterone have a highly elevated risk for endometrial cancer. Because of these data, conjugated estrogens are considered known human carcinogens (IARC V.21, 1979; NTP, 1998 [Report on Carcinogens, 8th ed.]). Unlike the breast, where tamoxifen is an anti-estrogen (used to treat breast cancer because of this property), it acts as an estrogen agonist in the uterus. Therefore, tamoxifen would likely produce the same effects as conjugated estrogens in the uterus. Available data strongly indicate that endometrial cancer following exposure to estrogens is caused by estrogen receptor-mediated responses. DNA adducts have not been detected in human samples (IARC V.66, 1996) with one exception where

low levels of DNA adducts were seen in leukocytes and endometrial tissue of breast cancer patients receiving tamoxifen (Hemminki et al., 1996, 1997).

In animal and *in vitro* experiments, tamoxifen readily forms DNA adducts in several tissues and cells, and either these adducts or the estrogenic activity of tamoxifen could be responsible for liver cancer observed in rodents exposed to tamoxifen.

Although tamoxifen is not mutagenic in bacteria, it is positive for micronuclei formation in human cells *in vitro* (Otto et al., 1996). *In vivo*, it increases aneuploidy and chromosomal aberrations in the livers of female Sprague-Dawley rats (Sargent et al., 1996).

Available data indicate that the receptor-mediated mechanisms involved in the carcinogenic actions of tamoxifen are operative in humans. Genotoxic mechanisms may also be operative in people, but preliminary studies suggest that they are quantitatively less than in rodents.

PROPERTIES

Tamoxifen is a white crystal from petroleum ether, with a melting point of 96-98 °C. Tamoxifen citrate ($C_{32}H_{37}NO_8$, mol. wt. = 563.65, CAS Registry No. 54965-24-1), the form of tamoxifen used in drug preparations, is a white, fine, crystalline powder. It is slightly soluble in water, and soluble in ethanol, methanol, and acetone. The compound is hygroscopic at high relative humidities, and sensitive to ultraviolet light. When heated to decomposition, Nolvadex® (tamoxifen citrate) emits toxic fumes of NO_x (HSDB, 1997; Lewis, 1992).

USE

Tamoxifen has proven to be a successful palliative therapy for advanced breast cancer yielding response rates similar to those seen with other endocrine treatments, but with few side effects. It has been commonly used as a primary therapy for breast cancer in elderly women who are considered poor candidates for surgery. Tamoxifen has been the adjuvant therapy of choice for postmenopausal, node-positive, and estrogen or progesterone receptor-positive women since the mid-1980s, and for postmenopausal, node-negative, and estrogen or progesterone receptor-positive women since the early 1990s. It is also being used in many cases of node-negative and receptor-positive premenopausal women. A high proportion (40-60%) of all women who undergo potentially curative surgery for breast cancer now receive adjuvant tamoxifen therapy for a period of 2 to 5 years (IARC V.66, 1996).

First approved for pharmaceutical use in the United Kingdom in 1973 and in the United States in 1977 (Diogenes, 1997), tamoxifen is presently registered in 97 countries. Tamoxifen use has been estimated at more than 7 million patient-years. The usual dose in the United States and the United Kingdom is 20 mg/day for 1 to 2 years whereas in continental Europe, usual doses are 30 to 40 mg/day (IARC V.66, 1996).

PRODUCTION

Tamoxifen is produced by treating 4-β-dimethylaminoethoxy-α-ethyldesoxylbenzoin with phenylmagnesium bromide or phenyllithium to form 1-(4-β-dimethylaminoethoxyphenyl)-

1,2-diphenylbutanol. Dehydration of the product yields a mixture of tamoxifen and its *E*-isomer, (*E*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]ethyldimethylamine, which may be separated with petroleum ether. For pharmaceutical preparations, tamoxifen is converted to the 1:1 citrate (Gennaro, 1995; cited by IARC V.66, 1996).

The U.S. and British pharmacopoeias limit the *E*-isomer to not more than 0.3% and 1%, respectively, in tamoxifen and tamoxifen citrate (IARC V.66, 1996).

Tamoxifen in pharmaceutical formulations is present as its citrate salt. Tamoxifen citrate is available as 15.2-, 30.4-, and 45.6-mg tablets. These correspond to 10, 20, and 30 mg of tamoxifen (IARC V.66, 1996).

Two suppliers of tamoxifen citrate are listed in the *Chemcyclopedia 1997* (Strum, 1996). The product Nolvadex® is marketed by Zeneca Pharmaceuticals (PDR, 1995).

Production of tamoxifen citrate worldwide increased from approximately 15,000 lb [7.0 metric tons (Mg)] in 1989 to 19,000 lb (8.5 Mg) in 1991, 22,300 lb (10.1 Mg) in 1993, and 22,700 lb (10.3 Mg) in 1995 (IARC V.66, 1996).

EXPOSURE

Tamoxifen is not known to occur as a natural product (IARC V.66, 1996). A U.S. National Institute of Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NOES) for 1981-1983 indicated that 350 employees were potentially exposed to tamoxifen in the workplace. Additionally, 2100 employees were potentially exposed to tamoxifen citrate (IARC V.66, 1996)

REGULATIONS

Tamoxifen citrate was first allowed on the U.S. market in 1977 (equivalent to 10 mg base). The June 1997 edition of the New Drug Application List (NDL) lists both 10-mg and 20-mg base forms with indications for the treatment of metastatic breast cancer in premenopausal women as an alternative to oophorectomy or ovarian irradiation and for the treatment of panic disorder, with or without agoraphobia. In 1986, it was allowed in postmenopausal women as a single agent to delay breast cancer recurrence following total mastectomy and axillary dissection. In 1989, it was allowed in premenopausal women as an alternative to oophorectomy or ovarian irradiation. In 1990, it was allowed in women with axillary node negative breast cancer. In 1993, tamoxifen was permitted to be used for the treatment of metastatic breast cancer in males. In 1994, the FDA established a new strength (20 mg) and dosage regimen (once or twice daily) (Diogenes, 1997).

California listed tamoxifen as a carcinogen in May 1995. The expert committee, established for Proposition 65, decided to let the public know that tamoxifen use is likely to cause endometrial cancer. Zeneca Pharmaceuticals, the supplier of Nolvadex®, did not challenge these findings (Mack, 1995). Regulations are summarized in Volume II, Table A-38.